The second group of patients studied by Small and colleagues had undergone both a physical and a psychiatric assessment before operation, but neither pre- nor postoperatively were the physicians and surgeons informed of the results of the psychiatric assessment. Of the 98 patients who came to surgery 65% were judged to be psychiatrically ill. Depression was diagnosed in 48 patients, anxiety in 41, and "character disorder" in 30. Three patients were psychotic. There was no evidence that the psychiatric patients came to surgery at an earlier stage in their ulcer history than did the normal patients. Thirty months after operation, the outcome, both physical and psychiatric, was assessed. Once again the age of the patient and the duration of his symptoms before operation were found to have had no significant influence on the results of surgery. Though psychoneurotic patients did less well than their stable brethren, 70% of them obtained clear benefit, and the better the physical result of surgery the greater was the chance of psychiatric improvement. Even better results might have been achieved, as the authors themselves state, if these patients had also received prompt psychiatric treatment. The subgroup which did least well consisted of patients who had psychiatric symptoms coupled with less severe ulcer disease.

This thorough, critical study raises many points of interest. The 65% incidence of psychoneurosis in patients coming to surgical operation for peptic ulcer is surprisingly high. Did the patients in the second group form a consecutive series or were they selected in any way? Or did the policy of "earning" the operation help to produce the depression and anxiety?

It is interesting that moderate or bad results were recorded in only three (13%) of the 23 patients who gave an ulcer history of less than five years, whereas no fewer than 17 (26%) of the 66 patients whose history was of more than 20 years had an unsatisfactory outcome to surgery. Furthermore, these data take no account of the greater morbidity and mortality to be expected from the operation in patients with a long ulcer history if only because they are older. Thus there is reason to believe that relatively early operation for duodenal ulcer may in fact yield better clinical results than an operation delayed so that the patient may "earn" it.

The authors conclude that "selection for operation by 'earning' is unreliable in that it fails to identify that group of patients liable to do badly." It follows that when a patient has an ulcer that is judged to be severe owing to complications or pain that is poorly relieved by medical measures he should be given the benefit of prompt elective surgery. This will save him suffering pain over the years and protect him from the hazards both of dangerous complications and of the resulting emergency surgery, which is often performed at night under unfavourable circumstances. In the industrial cities of Britain such operations are still being performed with depressing frequency on decrepit old men with emphysematous lungs and narrowed coronaries whose ulcer has been present for half a lifetime.

Progress in surgery for duodenal ulcer is possible only if the three main causes of its failure are clearly recognized and steps taken to avoid them. Operation fails because of recurrent ulceration, the side effects of the operation, or faulty selection of the patient for operation.[7] Considerable evidence is now available that the incidence both of incomplete vagotomy[8-10] (the usual cause of recurrent ulcer) and of postvagotomy diarrhoea[8 11 12] is greatly reduced if bilateral selective vagotomy is performed in preference to truncal vagotomy. A planned, elective approach is needed for this operation. Finally, it should be mentioned that when either selective or "highly-selective" vagotomy[13] is performed in the absence of pyloric stenosis the addition of pyloroplasty or gastrojejunostomy is probably unnecessary,[13 14] because gastric emptying is satisfactory without the drainage procedure. In this way side effects can be cut to a minimum—but only if the concept of "earning" is abandoned, so that elective surgery may be undertaken at a sufficiently early stage.

Sleeping Pills

In the *B.M.J.* this week Drs. J. I. Evans and O. Ogunremi describe at page 310 an investigation of some physiological features of sleep. They tested healthy volunteers after clinical doses of methaqualone 250 mg. plus dephenhydramine 25 mg. (Mandrax), chloral hydrate, and dichloralphenazone (Welldorm).

Sleep consists of two principal varieties, orthodox sleep and paradoxical (rapid eye movement, R.E.M.) sleep, which alternate during the night. In addition to rapid eye movements the rather dramatic features of R.E.M. sleep include irregular heart rate, breathing, and blood pressure; penile erection; and dreaming. Evans and Ogunremi pay especial attention to the proportion of R.E.M. sleep in the total night's sleep. They found a modest suppression of R.E.M. sleep by chloral hydrate 0·8 g. but little or none after dichloralphenazone 1·3 g. or Mandrax. A considerable reduction is to be expected after barbiturates.

Negative evidence of lack of distortion of normal sleep patterns should certainly be held to the credit of any hypnotic, but many criteria must be used in assessing merit in a drug. R.E.M. sleep itself can vary not only in duration (which is what Evans and Ogunremi measured) but also in intensity. Barbiturates[1 2] and glutethimide[3] reduce this intensity and cause eye movements to be sparse during periods of R.E.M. sleep. A Chicago team led by A. Rechtschaffen[4] have studied methaqualone, and, though also finding no effect on the duration of R.E.M. sleep, have found that the relatively small dose of 150 mg. decreased its intensity.

Apart from their effectiveness in inducing sleep, their differences in abuse potential, and their safety in overdosage,

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7 *British Medical Journal*, 1970, **2**, 492.

hypnotics must be assessed by the hangover they induce. This means more than just the patient's estimate, which can be highly unreliable, as A. Malpas and colleagues recently reported.[5] They gave nitrazepam, 5 or 10 mg., or amylobarbitone sodium, 100 or 200 mg., to normal volunteers. In the middle of the following day volunteers actually considered themselves more often "alert" after the drugs than after placebo, yet when objectively tested they performed much less sucessfully on motor tasks and drowsed off more readily when bored. These findings are all too reminiscent of the driver who, believing that he drives better after alcohol, ends in an accident.

We know little of the true functions of sleep, and recent knowledge of it shows it to be a complex state. Little is known either of the good or ill effects of hypnotic drugs, though their attractions as easy means of escape from reality are all too evident. The benzodiazepines seem at the moment to have low potential as drugs of abuse, so that nitrazepam, which has also the advantage of being remarkably non-toxic,[6] may be regarded as a reasonable choice when a hypnotic must be prescribed. But it has become increasingly clear that good clinical practice requires every doctor to undertake a searching review of his prescribing of hypnotic drugs.[7]

Trimethoprim–Sulphamethoxazole in Typhoid

Enteric fever obeys no therapeutic rules. Antibiotics such as chlortetracycline and streptomycin, which might from their *in vitro* activity be expected to exert some effect on it, do not. Still more might be expected of polymyxin, gentamicin, or cephaloridine, since they can kill typhoid bacilli in concentrations lower than that of chloramphenicol, which merely inhibits growth; yet A. T. Dawkins and R. B. Hornick[1] could achieve nothing by their administration in typhoid fever, even blood cultures remaining positive. Much was hoped of ampicillin, since it is as active as chloramphenicol by ordinary tests, bactericidal instead of merely bacteristatic, and safely administrable in much larger doses; yet results have been disappointing. Despite all these new discoveries chloramphenicol has remained the standard treatment in enteric fever for over 20 years.

Chloramphenicol has several serious drawbacks. It regularly produces defervescence, but relapse is common, and since there is no bactericidal effect the organism is not eliminated. A subsequent carrier state is common—some say actually favoured by the treatment. It carries a risk, however remote, of producing marrow aplasia. Moreover it seems that the effect of chloramphenicol is not what it used to be: studies from several countries report an extension of the period to defervescence from an original mean of about three days to six. Unfortunately none of these studies has included an examination of bacterial sensitivity to the drug; a gradual diminution might well acount for the present slower response of the disease. Clearly an alternative treatment free of these drawbacks would be a welcome advance.

It seems that this may have been found in trimethoprim plus sulphamethoxazole (Septrin, Bactrim), the synergically acting combination of synthetic antibacterial drugs with an already established place in the treatment of urinary, respiratory, and other infections. The range of activity of this combination is extensive. It includes the pyogenic cocci, but such infections are already well provided for by penicillin and other antibiotics. It also includes the enterobacteria, and these are in general less sensitive to antibiotics—hence the successful application of trimethoprim–sulphamethoxazole to urinary tract infections, most of which are caused by such organisms. Among enterobacteria are the *Salmonella* group, and these are highly sensitive to trimethoprim: 14 strains of different species were all inhibited by 0·06-0·25 μg./ml.[2] Since they are also at least moderately sensitive to sulphonamides the combination could reasonably be expected to have an effect on salmonella infections. This was apparently verified in a preliminary trial of the treatment of typhoid fever in Ibadan reported[3] in 1968, and a similar small-scale trial in Kampala[4] also gave encouraging results.

The first trial of this treatment on a full scale is described by S. A. Kamat on p. 318. From the vast numbers of patients in Bombay 220 men were chosen with positive blood cultures (*S. typhi* in 212 and *S. paratyphi A* in 8), thus leaving no doubt of the diagnosis. Of these 120 were treated with chloramphenicol in the usual doses and 100 with trimethoprim–sulphamethoxazole, three tablets being at first given twice a day; then the dose was reduced to two and found to have an equal effect. All the patients recovered without haemorrhage or perforation, which is characteristic of the disease in this area. There was little difference between the two groups in the period to defervescence, but in other features they differed considerably. Ten patients treated with chloramphenicol and none in the other group underwent a "toxic crisis." Initial "toxaemia" was rapidly relieved by trimethoprim–sulphamethoxazole but persisted longer (or even in 11 patients actually developed) during treatment with chloramphenicol. "Pronounced weakness and even prostration" were characteristic of the chloramphenicol group, weakness persisting for two to three weeks, but for only about one week in the other group. Observer bias could have entered into such a study, which was apparently in no sense blind, but it was on such a scale and the findings are so consistent that it must be accepted as evidence of the superiority of the new treatment over chloramphenicol in typhoid fever, at least as seen in this area. No observations were made on subsequent intestinal carriage.

Egypt is another country where the treatment of typhoid fever can be extensively studied, and a group of workers, including several from the U.S. Naval Medical Research Unit No. 3, which has been engaged there in such studies for a number of years, report briefly on p. 321 on the successful treatment with trimethoprim–sulphamethoxazole of eight cases of typhoid fever, five of paratyphoid A, B, or C, and two of acute brucellosis. They also testify to the rapid clinical improvement produced: "toxicity" and abdominal distension were relieved within 48 hours. There were no relapses and follow-up cultures were all negative. Though this trial was uncontrolled the authors' experience in this field is so extensive that their enthusiasm must command attention. A third contribution to the subject, on p. 316, is a study in Aberdeen of the treatment of carriers. Of four carriers of typhoid since the outbreak there in 1964 one man was cleared by a month's treatment with trimethoprim–sulphamethoxazole, and three women were not, but all three had radiological abnormalities

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